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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,358	07/02/2003	Reto Crameri	10806-93A	5425

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,358	CRAMERI ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-23* is/are pending in the application.

4a) Of the above claim(s) *20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/319,806.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/2/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response received August 24, 2006 is acknowledged.

Claims 1-13 have been canceled.

Claims 14-23 are pending in this application.

Applicant's election with traverse of Group I, claims 17-19 and linking claims 14-16, as they read on methods of diagnosing ABPA in vitro, and the species election of rAsp f4, in the reply filed on August 24, 2006 is acknowledged. The traversal is on the ground that there is no burden to the examiner in simultaneously searching all claimed inventions. This is not found persuasive because of the reasons of record set forth in the restriction requirement mailed June 28, 2006, wherein it is stated that the claimed inventions encompass distinct reagents and methodologies, that art applicable to one invention would not necessarily anticipate or render obvious the other invention, and that as such a thorough search of one invention would not be coextensive with the other invention which is further evidenced by their different classification. The species election of allergen has been extended beyond the elected species of rAsp f4 and was stopped upon the finding of other species.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in the reply filed on August 24, 2006.

Information Disclosure Statement

2. Applicant's IDS submitted 7/2/03 has been considered.

Claim Objections

3. Claims 14 and 19 are objected to because of the following informalities:

Claim 14, the only independent claim, recites the abbreviation "ABPA" but the claim does not recite the full name of the disease. For clarity, the claim should recite "allergic bronchopulmonary aspergillosis (ABPA)". Appropriate correction is required.

Claim 19 is objected to as being a duplicate of claim 18 since the claims do not appear to differ in scope since in both claims the only isotype recited is IgE.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

5. Claims 14-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The independent claim and all dependent claims are indefinite because as currently recited it is not clear if it is the antibody or the allergen that comprises the capacity to "discriminate with 100% specificity". Further, what is the relevance of patient antibodies such that a skilled artisan knows 100% of the time that a patient has a disease, ABPA for example, but does not have a different disease such as allergy? Are the antibodies present in ABPA but not allergy, or is diagnosis based upon some other relationship and factual circumstances?

Claim 18 is also indefinite in the recitation of "the IgE class, or IgE class, or subclasses thereof". The claim should not recite IgE twice, and there are no known subclasses of human IgE (Janeway et al., Figure 8.16 on page 8:19). Thus the metes and bounds of applicant's claimed invention are not clear.

Claims 18 and 19 are indefinite for the recitation of "antibodies of the IgE class are determined." How is an antibody "determined"? A skilled artisan would know how to detect the presence of an antibody and would also know how to identify the isotype and possible subtypes of said antibody, but such concepts are not clearly stated in the claims as presently written.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

7. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed a method based upon antibody binding to allergens that discriminates with 100% specificity between allergenic bronchopulmonary aspergillosis (ABPA) and allergic sensitization to *A. fumigatus*. A working example is disclosed wherein recombinant allergens Asp f4 and f6 are used to screen for reactive antibodies in sera obtained from ABPA and *A. fumigatus* allergy patients. The data disclosed indicate that antibodies to f4 and f6 were detected in the ABPA patients but were never detected in the *A. fumigatus* allergy patients. As such a method that uses allergens f4 or f6 to detect the presence of patient antibodies that bind said allergens discriminates with 100% specificity between ABPA and *A. fumigatus* allergy (see particularly Table 4 and lines 3-13 of page 15). The amino acid sequence for f4 and f6 are also disclosed by SEQ ID number (SEQ ID NO:4 and 2 respectively).

The breadth of applicant's claims is not limited to these two allergens, but encompass the use of any "ABPA-related recombinant allergen." It was known in the art that discriminating between ABPA and *A. fumigatus* allergy is difficult since antibodies to many *A. fumigatus* allergens are detected in both conditions (Little et al. and Moser et al., of record on the 7/2/03 IDS, see entire documents). Applicant's claimed method uses "ABPA-related recombinant allergens" for antibody binding, a genus of molecules of which *A. fumigatus* allergens are only a subset. The recited genus reasonably encompasses recombinantly made wild-type *A. fumigatus* allergens as well as derivatives which differ in sequence due to truncations, substitutions, and internal deletions, as well as molecules that cross-react with antibodies that are only

found in ABPA patients (see particularly lines 7-34 of page 4). The specification does not disclose any epitopes of *A. fumigatus* allergens that are bound by antibodies from ABPA patients but not *A. fumigatus* allergy patients and the specification does not appear to teach what structure or structures are required of molecules recognized only in ABPA patients.

Antibodies can bind a wide variety of structures, such as amino acids, nucleic acids, carbohydrates and small organic molecules (Janeway et al., pages 2:2-2:4). It is noted that "ABPA-related recombinant allergens" need not be polypeptides since other molecules, such as nucleic acids, can be made using recombinant techniques. It is known that all antigens (i.e. molecules that can be bound by antibodies) are not allergens, and that there is no art recognized method to distinguish allergic from non-allergic molecules on an *a priori* structural basis (Bumenthal et al., in Allergens and Allergen Immunotherapy, pages 37-50, see entire document, particularly the last sentence of the third full paragraph of page 39). Even when epitopes know to be important for binding to IgE have been identified, it is not predictable how changes to such sequence influence antibody recognition (Burks et al., Eur. J. Biochem, 1997, 245:334-339, see entire document, particularly the top right of page 338). Indeed, Colman teaches that even single amino acid changes to a polypeptide can completely abrogate antibody binding (of record on the 7/2/03 IDS, see entire document, particularly the paragraph that starts in the right column of page 33). The recombinant allergen that is used in the claimed method must be capable of binding to antibodies present in patient sera, wherein said patient generated an antibody response based upon a prior encounter with native *A. fumigatus* allergens. Given that the breadth of applicant's claims read on molecules that differ in sequence from native *A. fumigatus* polypeptides and the teachings of the art that even a single amino acid change in a polypeptide can eliminate antibody binding, it does not appear that the claimed method is predictable when using recombinant allergens that differ in sequence or structure from native *A. fumigatus* allergens.

Therefore, give the breath of applicant's claimed method, the limited number of working examples, the lack of guidance as to what structure must be maintained by

"ABPA-related recombinant allergens" for use in the recited methods, and the art recognized unpredictability in maintenance of antibody binding to non-identical structures, a skilled artisan would be required to engage in undue trial an error to make and use the full breadth of applicant's claimed invention.

8. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed a broad method that utilizes the genus of "ABPA-related recombinant allergens". The specification appears to teach that this genus of allergens can be used in diagnostic methods capable of discrimination with 100% specificity between ABPA and *A. fumigatus* allergic patients since antibodies that bind "ABPA-related recombinant allergens" are only found in ABPA patients and are never found in patients suffering from *A. fumigatus* allergy. The specification does not appear to explicitly define the term "ABPA-related recombinant allergens", but the disclosure indicates in lines 7-35 of page 4 that this term "includes any recombinant allergen, irrespective of origin" such as fragments of *A. fumigatus* allergens as well as "ABPA-related allergens and fragments derived from other sources, having one or more ABPA epitopes in common with an ABPA-related allergen from *A. fumigatus*." As such, the genus of "ABPA-related recombinant allergens" also reasonably encompasses variants of *A. fumigatus* allergens that differ in amino acids sequence from the naturally occurring *A. fumigatus* allergens by virtue of additions, truncations, internal deletions and amino acid substitutions which can be introduced into recombinant allergens. Applicant has not disclosed the structure (amino acid sequence) of any epitope of *A. fumigatus* allergens, and the only disclosed species that appear to support the recited genus of "ABPA-related recombinant allergens that discriminate with 100% specificity" appear to be rAsp f4 and rAsp f6 can be used in methods which discriminate between

the two patient populations with 100% specificity (see Table 4 and lines 3-13 of page 15).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court held that disclosure of a single member of a genus (rat insulin) did not provide adequate written support for the claimed genus (all mammalian insulins). It should be noted that the specification discloses that rAsp f4 and f6 have different sequences and are different size proteins (40 and 28 kDa respectively) and presumably have different biological activities in *A. fumigatus*, and as such differ much more from one another than the genus of all mammalian insulins. Further note that f4 and f6 do not appear to share any common structure, and no common structure appears to be disclosed for the genus of "ABPA-related recombinant allergens". As such, f4 and f6 are not a representative number of species of the recited genus, and the only function is that the genus of allergens can be bound by antibodies. In Lily, the court also noted:

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material

generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Therefore, it appears that the broad genus of "ABPA-related recombinant allergens" lacks adequate written description because there does not appear to be any correlation between structure and function. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of "ABPA-related recombinant allergens" at the time the instant application was filed.

9. Claims 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 14-19 are not claims as originally filed in parent application 09/319,806, of which the instant application is a continuation. In the remarks received 7/2/03 applicant indicates that claims 14-17 recite limitations from original claims 1-3 and 6. These claims do not appear to recite the limitation "which discriminate with 100% specificity between ABPA and allergic sensitization to *A. fumigatus*." The specification discloses in Table 4 and in lines 3-13 of page 15 that 100% specificity can be obtained by use of recombinant Asp f4 and f6. This disclosure does not indicate that any other allergens can be used in methods that discriminate between the two patient populations with 100% specificity. As such, the instant claims have combined a limitation of two specific species (100% specificity) to the broad genus of "ABPA-related recombinant allergens". The specification does not appear to teach that this broad genus comprises the recited

limitation, and as such applicant's claim amendments received 7/2/03 have introduced new matter into the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borga, (Ph.D. dissertation from the Karolinska Institute, 1990) in view of Moser et al. (of record as reference ab on the 7/2/03 IDS).

Borga teaches methods of detecting IgE antibodies that bind *A. fumigatus* allergens using in vitro immunoassays (see dissertation abstract). Borga identified 8 allergens that were only recognized by ABPA patients and 4 allergens which were only recognized in *A. fumigatus* allergy patients, and teaches that such differences are of diagnostic value (see particularly from line 36 of page 17 to line 15 of page 18 of the instant specification and the dissertation abstract). Note that these allergens of Borga discriminate with 100% specificity since the patterns of reactivity are patient-specific (see lines 12-15 of page 18 of the specification). Some of the allergens identified by Borga are disclosed as being intracellular (see dissertation abstract). These teachings differ from the instant claimed invention in that Borga did not produce recombinant forms of his *A. fumigatus* allergens.

Moser et al. teach that the use of recombinant allergens in diagnostic assays offer the advantages of increased standardization and reproducibility over allergen extracts prepared from biological materials (see entire document, particularly the right column of page 2 and the last paragraph of the Discussion section).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to perform the diagnostic method taught by Borga using recombinant allergens. Motivation to do so comes from the teachings of Moser et al. that recombinant allergens are better for diagnostic assays because they offer the advantages of increased standardization and reproducibility when performing such assays.

It is noted that applicant has discussed at length the teachings of Borga in the instant specification yet has not submitted said reference on an IDS in this application. The examiner was able to locate the abstract of the dissertation but was not able to locate the full text of the document. Applicant is requested to submit a complete copy of the dissertation by Borga as part of the response to this office action so that the dissertation can be examined for other issues material to the patentability of the instant claimed methods.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 14-19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7, 8, and 12-16 of U.S. Patent No. 6,830,891. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented methods of diagnosing ABPA recite specific allergens, namely rAsp4, rAsp6, and rAsp8, and thus anticipate the instant methods of diagnosing ABPA that recite the genus of "ABPA-related recombinant allergens". Note that these allergens discriminate with 100% specificity between ABPA and allergic sensitization (see Table 4 in column 12 and lines 17-27 of column 8).

14. No claims are allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
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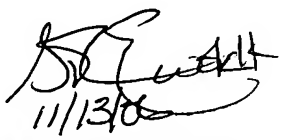
Technology Center 1600
November 6, 2006



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